UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/007,010	12/04/2001	Alexander H. Borchers	RTS-0345	7968

7590 08/08/2002

Jane Massey Licata
Licata & Tyrrell, P.C.
66 East Main Street
Marlton, NJ 08053

EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/08/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/007,010	Applicant(s) BORCHERS ET AL.	
	Examiner Jane Zara	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). 5 .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *2 Accessions* .

DETAILED ACTION

This Office action is in response to the communication filed May 10, 2002, Paper No. 4.

Claims 1, 2, 4-20 are pending in the instant application.

Election/Restriction

The election requirement made on May 10, 2002, by phone to Applicants' representative, Jane Massey-Licata, has been rendered moot in light of the amendment filed May 10, 2002 and the election requirement is hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro inhibition of expression of hematopoietic cell protein tyrosine kinase (hck) comprising the administration of antisense oligonucleotides which specifically target the nucleic acid encoding hck, does not reasonably provide enablement for the in vivo inhibition of expression of hck, nor any treatment or prevention effects for any conditions or diseases associated with hck expression in an organism. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods of inhibiting the expression of hematopoietic cell protein tyrosine kinase (hck) comprising the in vitro or in vivo administration of antisense oligonucleotides between 8 and 50 nucleobases in length, whereby treatment or prophylactic effects are provided in an organism for any disease or condition associated with the expression of hck, and which diseases or conditions include hyperproliferative disorders (e.g. cancer including leukemia), inflammation, diabetes and viral infections.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of antisense treatment in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). The high level of unpredictability regarding the prediction of antisense efficacy in treating disease states was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found more successful than antisense treatment (BioWorld Today: See entire

article, especially paragraphs 3 and 5-7 on page 1). Additionally, Palu et al teach that the success of gene delivery using virally derived vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2.)

Tamm et al, in a review article discussing the therapeutic potential of antisense in treating various forms of neoplasia, conclude that "Proof of clinical efficacy, of any of the antisense oligonucleotides in the field of oncology, is still missing." (see especially pages 490-493 for a summary of various clinical trials in process using antisense). Additionally, Agrawal et al point to various factors contributing to the upredictability of antisense therapy, including non-antisense effects attributed to secondary structure and charge, as well as biological effects exerted by sequence motifs existing within the antisense sequences, all providing for unpredictable in vivo side effects and limited efficacy (e.g. see pages 72-76). Agrawal et al speak to the unpredictable nature of the antisense field thus: "It is therefore appropriate to study each antisense oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide." (see page 80). Cellular uptake of antisense oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of antisense oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; see Chirila et

al in its entirety, especially pages 326-327 for a general review of the "important and inordinately difficult challenge" of the delivery of therapeutic antisense oligonucleotides to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of inhibiting the expression of hck in vivo comprising the administration of antisense oligonucleotides, nor has any guidance been provided for treating or preventing any disease or condition associated with hck expression, comprising the administration of antisense.

The specification teaches the inhibition of expression of hck encoded by SEQ ID NO: 3 in vitro comprising the administration of antisense oligonucleotides between 8 and 50 nucleobases in length. The specification fails to teach the inhibition of hck expression in vivo, and the specification fails to teach the treatment or prevention of any disease or condition associated with the expression of hck comprising the administration of antisense oligonucleotides. One skilled in the art would not accept on its face the examples given in the specification of the in vitro inhibition of hck expression as being correlative or representative of the successful inhibition of hck expression in vivo comprising the administration of antisense oligonucleotides, nor of being correlative or representative of the successful treatment of any and/or all conditions or diseases in an organism associated with hck expression comprising the administration of antisense oligonucletoides in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the efficacy of antisense in

inhibiting a target gene in an organism, and further whereby treatment effects are provided. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery and treatment effects provided by antisense administered, and specifically regarding the instant compositions and methods claimed, which treatment methods are for any diseases or conditions associated with hck expression in an organism.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to methods of inhibiting the expression of hematopoietic cell protein tyrosine kinase (hck) comprising the in vitro or in vivo administration of antisense oligonucleotides between 8 and 50 nucleobases in length, whereby treatment or prophylactic effects are provided in an organism for any disease or condition associated with the expression of hck, and which diseases or conditions include hyperproliferative disorders (e.g. cancer including leukemia), inflammation, diabetes and viral infections. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring nucleic acids encoding hck whereby hck expression is inhibited in vivo, and further that treatment effects are provided for any and/or all diseases or conditions associated with hck expression in an organism. Since the specification fails to provide any particular guidance for the inhibition of hck expression in vivo comprising the administration of antisense, or for the successful prevention or treatment of any and/or all

conditions or diseases associated with hck expression in an organism, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the broad scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Matsubara et al.

Matsubara et al teach an antisense oligonucleotide between 8 and 50 nucleobases in length which specifically hybridizes to and inhibits the expression of hck encoded by SEQ ID NO: 3 (See the accompanying nucleic acid sequence alignment data of Matsubara et al: Only the alignment data has been provided for Matsubara et al, because the document, WO/95/14772, is 2245 pages in total. A full copy of the document will be provided, however, upon request by the Applicant.)

Claims 1, 2, 4, 5, 11, 12, 14 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Wei et al.

Wei et al (IDS document "AP", filed December 4, 2002, as part of Paper No. 3) teach compositions and methods comprising the administration of a phosphorothiolated antisense oligonucleotide between 8 and 50 nucleobases in length which specifically targets and inhibits the expression in vitro of the nucleic acid SEQ ID NO:3 which encodes human hck, and which compositions further comprise a pharmacologically acceptable carrier (see first full paragraph in right column on page 5156; last paragraph on page 5157- first paragraph on page 5158; figure 5 on page 5159).

Claims 1, 2, 4-14 are rejected under 35 U.S.C. 102(b) as being anticipated by McCay et al.

McCay et al teach compositions comprising an antisense oligonucleotide between 8 and 50 nucleobases in length which specifically hybridizes to and inhibits the expression of SEQ ID NO:3, and which antisense oligonucleotide optionally comprises modified internucleotide linkages including phosphorothioate linkages, modified nucleobases including 5-methylcytosine, modified sugar moieties including 2'-O-methoxyethyl sugars, and wherein the antisense is optionally a chimeric oligonucleotide, and which compositions further comprise a colloidal dispersion system and a pharmaceutically acceptable carrier (See especially nucleic acid sequence alignment data with SEQ ID NO: 31 of McCay et al; see also col. 6, line 29 through col. 15, line 10; col. 20, line 18 through col. 24, line 67).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wei et al, McCay et al and Matsubara et al as applied to claims 1, 2 and 4-15 above, and further in view of Quintrell et al and Lichtenberg et al and Milner et al insofar as the claims are drawn to compositions and methods for the in vitro inhibition of human hck expression comprising the administration in vitro of antisense oligonucleotides between 8 and 50 nucleobases in length which target and specifically hybridize with nucleic acids encoding human hck (of SEQ ID NO: 3), and which antisense oligonucleotides optionally further comprise internucleotide, nucleobase

and sugar modifications, or are optionally chimeric oligonucleotides, and which compositions further comprise a colloidal dispersion system and a pharmaceutically acceptable carrier.

Wei et al, McCay et al and Matsubara et al are relied upon as cited in the 102 rejections above.

The primary references do not teach the design and assessment of antisense oligonucleotides, which span the nucleic acid sequence encoded by SEQ ID NO: 3, in their ability to target and inhibit the expression of hck in vitro.

Lichtenberg et al (IDS document "AF", filed December 4, 2002, as part of Paper No. 3) and Quintrell et al (IDS document "AJ", filed December 4, 2002, as part of Paper No. 3) teach nucleic acid sequences encoding human hck (See especially figure 1 on page 2269 of Quintrell et al and 6 on page 854 of Lichtenberg et al).

Milner et al teach methods of designing and testing antisense oligonucleotides for their ability to specifically hybridize and inhibit the expression of a target nucleic acid of known nucleotide sequence (See especially figures 5-7 on pages 539-540).

It would have been obvious to one of ordinary skill in the art to inhibit the expression of human hck of known nucleotide sequence in vitro using antisense oligonucleotides which target and specifically hybridize with nucleic acid of SEQ ID NO: 3, encoding human hck, because the inhibition of a target gene of known sequence using antisense oligonucleotides, including those with nucleobase, internucleotide linkage and sugar modifications, has been taught previously by many including McCay et al and Milner et al. Milner et al additionally teach methods of

designing and evaluating antisense which target different regions of a target gene of previously disclosed sequence for their ability to inhibit a target gene. One of ordinary skill in the art would have been motivated to inhibit the expression of hck using antisense oligonucleotides because it had been taught previously by Quintrell et al and Lichtenberg et al that hck is a member of the SRC proto-oncogene family and hck plays a role in hematopoietic cellular differentiation and has been associated with the process of neoplastic transformation. One of ordinary skill in the art would have expected that antisense oligonucleotides which inhibit the expression of hck be used as a tool in investigating the role of hck in the processes of cellular differentiation and neoplastic transformation, and one of ordinary skill in the art would have expected that the inhibition of aberrant overexpression of hck using antisense oligonucleotides would provide potential therapeutic applications for such antisense. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be

retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J Zara
TC 1600

JZ

August 2, 2002